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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/721,864	11/24/2000	David Scheinberg	D6126	4077

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/721,864	SCHEINBERG ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4 and 7-22* is/are pending in the application.

4a) Of the above claim(s) *8-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claim 5.

Accordingly, claims 1, 3-4, 7 are examined in the instant application.

This application contains claims drawn to an invention nonelected with traverse in Paper No.5. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

MISCELLEANUOUS

It is noted that the clean version of claim 1 is different from its marked up version.

OBJECTION

Claim 1 is objected to because "a specific binding sites" is grammatically incorrect.

REJECTION UNDER 35 USC 112, SECOND PARAGARPH, NEW REJECTION

Claims 1, 3-4, 7 are indefinite for the use of the language "high specific activity" in claim 1, which is a relative term. The term "high specific activity" in claim 1 is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and

one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

REJECTION UNDER 35 USC 112, FIRST PARAGARPH, NEW MATTER, NEW REJECTION

1. Claims 1, 3-4, 7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 3-4, 7 is drawn to a method of killing a solid tumor more than 1 mm in size in a human, comprising 1) selecting a value for a high specific activity from a range of specific activies for an alpha particle-emitting isotope/antibody construct, wherein the antibody targets a specific binding site on a tumor cell, and is conjugated to the isotope, and wherein said range of specific activities is such that the value selected is "at least" sufficient for a pharmacologically effective amount of a dose of said construct to provide an amount of antibody to bind to a plurality of target sites on the tumor cell, wherein "at least" one alpha track per tumor cell is delivered thereto from said isotope upon binding of the antibody, 2) systemically administering a dose of said high specific activity construct to said human, and 3) repeat said administration wherein each repetition further reduces the size of tumor, thereby killing the tumor.

The specification does not disclose a selected value for a high specific activity, which is "at least" sufficient for a pharmacologically effective amount of a dose of the

construct to provide an amount of antibody to bind to a plurality of target sites on the tumor cell, wherein "at least" one alpha track per tumor cell is delivered thereto from said isotope upon binding of the antibody.

2. Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 7 is drawn to a method of killing a solid tumor more than 1 mm in size in a human, comprising systemically administering a dose of a high specific activity alpha particle-emitting isotope/antibody construct to said human, wherein said dose is from about 0.1 mg/m^2 to about 25 mg/m^2.

The specification does not disclose the specific dose of 25 mg/m^2.

REJECTION UNDER 35 USC 112, FIRST PARAGARPH, SCOPE, NEW REJECTION

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing a solid tumor more than 1 mm in size in a human, comprising systemically administering a dose of an alpha particle-emitting isopitope/antibody construct to said human, wherein at least one alpha track per tumor cell is delivered thereto from said isotope upon binding of the antibody, and wherein the range of specific activity of said construct is about "10 mCi/mg" to about 30 mCi/mg, does not reasonably provide enablement for a method of killing a solid tumor more than 1 mm in size in a human, comprising systemically administering a dose of an

alpha particle-emitting isopitope/antibody construct to said human, wherein at least one alpha track per tumor cell is delivered thereto from said isotope upon binding of the antibody, and wherein the range of specific activity of said construct is about "0.1 mCi/mg" to about 30 mCi/mg. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 7 is drawn to a method of killing a solid tumor more than 1 mm in size in a human, comprising 1) selecting a value for a high specific activity from a range of specific activities for an alpha particle-emitting isotope/antibody construct, wherein the antibody targets a specific binding site on a tumor cell, and is conjugated to the isotope, and wherein said range of specific activities is such that the value selected is "at least" sufficient for a pharmacologically effective amount of a dose of said construct to provide an amount of antibody to bind to a plurality of target sites on the tumor cell, wherein at least one alpha track per tumor cell is delivered thereto from said isotope upon binding of the antibody, and wherein the the range of specific activity is about "0.1 mCi/mg" to about 30 mCi/mg, 2) systemically administering a dose of said high specific activity construct to said human, and 3) repeat said administration wherein each repetition further reduces the size of tumor, thereby killing the tumor.

The specification discloses that for a cell line expressing about 10,000 binding sites, e.g. HL60, a minimum specific activity of 10 mCi/mg is needed to deliver 2 Bi-213 or Bi-212 atoms per cell so that at least one alpha particle is tracked through the cells (p.16, lines 1-13, and p.36, lines 3-4.

One cannot extrapolate the teaching in the specification to the claims, because as disclosed by the specification a minimum specific activity of the construct of 10 mCi/mg is needed to deliver one alpha particle per cell for a cell line expressing 10,000 binding sites on its cell surface, and because a specific activity of 0.1 mCi/mg is 100 times less than the required 10 mCi/mg disclosed by the specification, and it is unpredictable that there exists a tumor cell that has as much as 1,000,000 binding sites, in view that the HL60 cell line expresses only about 10,000 binding sites, as disclosed in the specification, and the SP2/Tac cell line disclosed by Hartman et al only expresses 18,000 binding sites (Hartmann et al, of record, p. 4363, first column, end of first full paragraph).

In view of the above, it would be undue experimentation to practice the claimed invention as broadly as claimed.

REJECTION UNDER 35 USC 103

Claims 1, 3-4, 7 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Simonson et al, 1990, in view of Kasperson, FM et al.

Applicant argues that Simonson et al do not teach or suggest further doses to effect "a cure" in their murine model. Applicant argues that Simonson et al consider administration of a large single dose to be equivalent to consecutive multiple doses to reduce tumor burden. Applicant argues that thus one could consider Simonson et al to have administered one dose in four partial doses. Applicant argues that Simonson et al teach that the efficacy of the Bi-212 labeled B72.3 antibody is reduced because 1) the

antigen is secreted and is not a surface antigen, 2) at 7-13 days the solid tumor was large and well-established, and 3) ascites do not form until well after establishment of the solid tumor. Applicant asserts that Simonson et al hypothesize that Bi-212 may be effective against peritoneal/ascetic cancers if ascites form sooner while any solid tumor is smaller. Applicant asserts that at most there is suggestion to try a Bi-212 labeled antibody targeted to a cell surface antigen on a smaller peritoneal tumor, which teaches away from the instant invention.

Applicant asserts that the Examiner states that the tumors taught by Simonson et al are peritoneal tumors and line the intraperitoneal cavity. Applicant asserts that Simonson et al teach that at the time of dissection of the mice, the tumor has spread over the internal organs and along the lining of the peritoneum. Applicant concludes that what Simonson et al consider as a large solid tumor weighing 3 gm could actually be a paper thin tumor covering a large intraperitoneal area.

Applicant argues that Kasperson et al teach that Bi-213 may have limited applicability in the treatment of solid tumors. Applicant asserts that this statement is reinforced when considering, that despite safer and easier production of Bi-213, Bi-213 has a half life about 33% longer than that of B-212. When specific activity is not taken into consideration and administration is contemplated only once, it is therefore not as effective as Bi-212 under these conditions.

Applicant further argues that as demonstrated with Hartmann et al, the specific activity of the Bi-212 construct in Simonson et al varied between 5-10 uCi and may be insufficient to form a minimally high specific activity construct. Applicant argues that

there is no suggestion is found that the inability to cure the tumor is due to an insufficient specific activity for the Bi-212/antibody construct used. Applicant argues that not only the Bi-212 construct taught by Simonson et al is administered intraperitoneally, but the antibody is targeted to a secreted antigen. Applicant asserts that the claimed invention works because the alpha-emitting construct is administered systemically, targets the cell surface directly, and can deliver at least one alpha tract to a cell.

Applicant's arguments in paper No:12 have been considered but are found not to be persuasive for the following reasons:

It is noted that the claims are not drawn to a "cure", rather the claims are drawn to "killing". In the absence of a definition of killing in the specification, and for the purpose of compact prosecution, it was and is assumed that "killing" refers to killing tumor cells within the tumor.

Contrary to Applicant's assertion that Simonson et al do not teach or suggest further doses to effect a cure in their murine model, Simonson et al teach both single and repeated administration of Bi-212 labeled antibody, wherein a 56% reduction in tumor mass is obtained (p.986s, first column, third paragraph and figure 1 on page 986s). The repeated administration taught by Simonson et al is not any different from the claimed repeated administration. Further, it is routine in the art to administer a therapeutical agent in multiple doses to increase the effectiveness of treatment.

In addition, contrary to Applicant's assertion, Simonson do not teach away from the invention, because it is clear that the method taught by Simonson et al successfully results in a 56% reduction in tumor mass, which could be as large as 3gm on average.

In addition, Simonson et al suggest of the use of an antibody targeting cell surface antigen, and treatment of smaller tumor, which would have been expected to be even more effective.

Concerning the size of the tumor taught by Simonson et al, it is noted that the Examiner did not recite that the tumors taught by Simonson et al are peritoneal tumors and line the intraperitoneal cavity. Although Simonson et al teach that at the time of dissection of the mice, the tumor has "spread over" the internal organs and along the lining of the peritoneum, it is noted that the tumors taught by Siimonson et al comprise both ascites (non-solid) and solid tumors, wherein it is well known in the art that ascites are fluid-like and thus could easily spread like a fluid. It is further noted that there is no reference recited by Applicant to document the "paper thin" properties of the solid tumors taught by Simonson et al, and to substantiate Applicant's assertion that the large solid tumor taught by Simonson et al could actually be a paper thin tumor covering a large intraperitoneal area.

Concerning the high specific activity, it is noted that Applicant claims a range of high specific activity of about 0.1 mCi/mg to about 30 mCi/mg. The specific activity of 5 to 10 mCi/mg taught by Simonson et al is certainly within the range of the claimed high specific activity, and thus is expected to deliver at least 1 alpha track per cell.

Concerning the use of Bi-213, although Bi-213 has a half life about 33% longer than that of Bi-212, this would not necessarily negate the obviousness for the use of Bi-213, because it can be an alternative to Bi-212, being safer and easier to produce than B-212, as taught by Kasperson et al, especially in view of the fact that the specific

activity of the construct taught by the combined prior art is within the range of the claimed specific activity, and that the administration of the construct could be repeated as taught by Simonson et al. Further, although Kasperson et al teach that Bi-213 may have limited applicability in the treatment of solid tumors, Kasperson does not teach that Bi-213 cannot be used for treating solid tumors. Thus in view of the fact that Bi-212 could be used successfully for treating large solid tumors, as taught by Simonson et al, and in view of the suggestion by Kasperson et al that Bi-213 can be an alternative to Bi-212, being safer and easier to produce than Bi-212, one of ordinary skill in the art would have expected that a construct of Bi-213/antibody specific for a solid tumor could be successfully used for treating solid tumors greater than 1 mm in size in diameter.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

April 22, 2004

SUSAN UNGAR, PH.D
PRIMARY EXAMINER